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# Capital Efficiency for Development Stage Biotech-based Firms: An IPO Perspective

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***Abstract*--Access to multiple tranches of capital is critical for predominantly no revenue development stage biotech firms. While financing needs are monotonically increasing over multiple years in the product development approval cycle, the market for high risk, milestone driven biotech investment is significantly more volatile than the financial markets as a whole. In this paper, we analyzed the role and relative importance of global biotech IPOs, as well as other sources of capital such as strategic alliances, for research and development funding. We also explored and assessed the degree of mismatch between the access to capital, operational efficiencies, and how firms solve the potential unmet capital requirements. Implications for investors, as well as small and large biotech company managers, is discussed.**

## I. Introduction

Development stage biotechnology companies which exploit emerging scientific insights such as genomics require significant risk-based capital to drive significant wealth, employment, and global competitiveness, particularly in the context of internationally recognized intellectual property (IP) exemplified by the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement. On the one hand, biotechnology product development is characterized by long product development life cycles with episodic and binary "stage-gate" project risk. Specifically, biotechnology project risk tends to monotonically decrease, while significantly increasing absolute capital requirements with each stage in the product development cycle. On the other hand, however, access and the cost of capital is significantly volatile and binary (i.e., financing windows for largely no revenue biotechnology firms are dependent on macroeconomic market conditions), particularly so in the initial public offering (IPO) market which represents a transformational stage in the development of early stage biotechnology firms.

In this paper, we analyzed the 1,255 global biotechnology IPOs completed during period 1994-2018 to examine the role of IPOs in the access to research and development capital. We also explored and assessed the degree of mismatch between the access to capital, operational efficiencies, capital market volatility, and valuation uncertainty. In addition, we will discuss implications for investors and policy makers, and development stage biotechnology firms require agility, including strategic alliances development, to ensure access to capital to foster continued progress in breakthrough treatments for unmet medical needs.

## II. Biotechnology Science As A Business

Biotechnology may be defined as "the use of cellular and bimolecular processes to solve problems or make useful products"[1]. A bioscience business model describes how firms enable innovative capacity from proprietary intellectual property and knowhow to effectively and efficiently create, deliver and capture value. Human therapeutics has been the largest segment of the biotechnology industry. The US Food and Drug Administration (FDA) approved the first biotechnology drug in 1982. Since then, the biopharmaceutical industry comprised of 708 publicly-traded companies with 203 thousand employees has realized over 250 drugs approvals, generating $139 billion in sales and market capitalization of $862 billion in 2016 [2]. As fully integrated biotechnology giants such as Amgen, Gilead, Regeneron and Biogen have emerged, the market valuation of the biotechnology industry has recently surpassed pharmaceutical firms. Indeed, the success of biotechnology has spurred the transformation of traditional pharmaceutical companies into biopharma companies through strategic alliances [3], notably blockbuster acquisitions such as Roche's purchase of biotech pioneer Genentech for $46 billion in 2009; or Johnson & Johnson's acquisition of Actelion for $30 billion in 2017. As prominent researcher Martine J. Piccart-Gebhart noted at the 41st Karnofsky Memorial Award Lecture:

> *"The pharmaceutical industry is under extreme financial pressure…Given increasingly cost-constrained health care systems, limited patent durations on blockbuster drugs, competition from generics, a more demanding regulatory environment, diminishing marketing exclusivity, and progressively smaller markets resulting from the rapidly increasing molecular segmentation of the populations of patients…companies are being forced to overhaul their drug development strategies.* [4]

Of note, large pharmaceuticals accounted for 70% of new drug approvals over the 2010-2014 period, but decreased to 37% in 2018 [5].

### *A. Biopharma industry is significantly disrupted by genomics*

Scientific insights from biotechnology largely driven by government and institutional support such as genomics has spurred the ability of researchers in academia and industry to

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address critical areas of unmet medical need such as rare diseases and Alzheimers [6]. For example, the development of gene editing using CRISPR (clustered regularly interspaced short palindromic repeats)//Cas9 (enzyme that uses CRISPR sequences to recognize and cleave specific strands of DNA (deoxyribonucleic acid)) system by Jennifer Doudna and Emmanuel Charpentier has rapidly spurred wide interest in gene editing for agriculture, diagnostics and therapeutics, as well as new company formation such Intelia[7], CRISPR Therapeutics and Editas. So-called new biology approaches such as gene therapy and editing has driven a fundamental shift in drug development towards narrowing patient populations defined by molecular targeting versus clinical presentation. In 2017, Merck's Keytruda (pembrolizumab) was the first product was approved for any cancer with the molecular target PD-1 (programmed cell death receptor) [8]. The practical effect of this phenomena is that pharmaceutical companies must reinvent and transform themselves from blockbuster dependent, multi-billion drugs to orphan diseases (see Figure 1) [9].

### *B. Intellectual property (IP) strengthens the value of exclusivity amidst rising development costs*

Likewise, the global recognition of intellectual property (IP) has accelerated the pace and intensity of company formation, capital allocation and market valuation. The global IP regime, exemplified in the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), negotiated during the 1986-94 Uruguay Round, introduced intellectual property rules (e.g., harmonization of patent life to 20 years) into the multilateral trading system for the first time [10]. The practical result of multilateral IP recognition is that research from any country can compete for capital and development resources [11].

Despite this significant investment, productivity over the years has been decreasing, with higher costs of drug research and longer clinical development timelines. The average drug takes over $2.6 billion and 12 years to go from laboratory to approval. Part of the reason for rising development costs is the high failure rate of product candidates in clinical trials due to increasingly specific molecular targets for unmet diseases—which necessarily increases development risk, complexity of biologic systems with compensating mechanisms, overlapping intellectual property claims, and shifting regulatory requirements. For the drug candidates that progress from animal testing into human clinical trials, the overall success rate is 11 percent. In other words, nearly nine out of every ten products entering clinical trials will fail, and some disease areas are proving to be even more challenging, for instance, oncology success rates are approximately 5 percent. Furthermore, getting approval is no guarantee of commercial success. To date, only four of ten products that reach the market achieve profitability. This lack of development productivity (either increasing the value created or decreasing the time required to create value) has taken its toll on industry financial performance. Out of the nearly 350 publicly traded biopharmaceutical companies, only a small minority have reached sustainable profitability. The heavily regulated, high complexity biopharmaceutical environment characterized by binary risk, disproportionately impacts the sustainability of start-ups [12].

### *C. No revenue, development stage biotech firms face significant access to capital volatility*

Notwithstanding, a critical and somewhat unique feature of the biotechnology industry is the significant amount of value that can be generated during various phases of product development that is reflected in the ability of start-up companies to raise successive rounds of private and public capital well advance of achieving sales or net income. Significant value can be created in terms of successive private rounds of financing at increasing enterprise valuations, obtaining liquidity by accessing public capital markets (e.g., IPOs, follow on offerings), as well as by executing trade sales and alliances with larger biopharmaceutical companies years before realizing sales and profitability. In this context, development stage biotechnology firms represent real options—defined as the right but not the obligation to make a series of business decisions (e.g., incrementally invest to advance a drug candidate from Phase 1 (safety), Phase 2 (preliminary efficacy), to Phase 3 (statistically significant efficacy and safety) [13].

The irregular nature of biotechnology financial markets, often characterized as "financing windows," increases operating risk and uncertainty (e.g., IPOs not being effective during a general market downturn) [14]. As a result of large capital requirements, long lead times, and episodic successes and failures, biotech financing cycles have been characterized by periods of high euphoria, only to be followed by deep disillusionment after a cluster of high-profile product failures occur or a macroeconomic shock (e.g., currency crisis, recession). This subjects early stage companies to high degrees of financing risks, regardless of their operational progress. While the industry has matured, the predominant venture capital financing model—one product platform or one product, in which a few investors who provide seed capital, and a long incubation period leading to sale or an IPO—has not markedly changed, despite modest overall risk-adjusted rates of return [12].

Public financing, on the other hand, is achieved by selling newly issued shares in a publicly traded company to individual and institutional investors (e.g., mutual funds, hedge funds). IPOs enable trading liquidity, and access to larger and deeper pools of financing. IPOs are the initial sale of stock that transforms a private company into a public company with financial disclosures and filings as required by the US Securities Exchange Act of 1934. While biotech IPOs are open to a small number of firms that can achieve successive rounds of venture capital and justify the large underwriting costs of investment banks, development stage R&D firms have also proven to be difficult to price and exhibit extraordinary volatility[15]–[18] despite investment syndicates, strategic alliances, or other signaling mechanisms [14], [19]. Of note, IPOs underwritten by larger, more prestigious banks

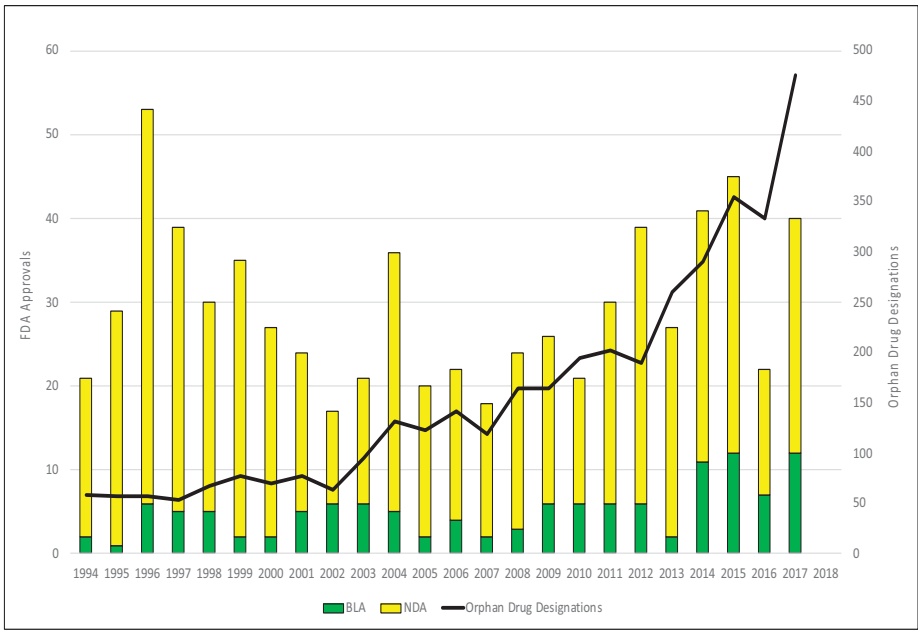


Figure 1: FDA Orphan Drug Designations (ODD) and Approvals (Biologics and Drugs)

outperform in terms of pricing and volatility suggesting a positive selection bias [20], [21].

IPOs have different pros and cons based on company and market's conditions. Once a company goes public, it can raise more funds in the future by secondary offerings as it has already access to the public markets. Furthermore, companies can increase their equity base, exposure, prestige, and public image while enabling cheaper access to capital and better management and employees enabled with liquid equity participation.

IPOs are also known to have facilitated acquisitions through using shares in acquiring other firms. IPOs may come with some disadvantages too as they are expensive and maintaining a public company adds extra costs in legal, accounting, and marketing areas [22].

Companies may also have less privacy as they need to disclose financial and business information and some of their business strategies may be exposed to the competitors in their SEC reports. Finally, the leadership and governance through board of directors may decrease company's and manager's risk-taking abilities while coping with lawsuits and legal actions related to their public shares can deem expensive and distracting.

Valuing an early-stage company or IPO is an arduous task due to the fact that company's current value depends on expected future revenues from products or services that have not been marketed yet [16]. Biotech firms are different than other industries in their IPO as they have higher revenue growth, issue a smaller fraction of their shares to investors, are more likely to be financed by venture capitalists, are issued when market returns are higher, have higher total offer value and first-day market value, and are supported by underwritten by high-ranking underwriters [16]. The percentage of filing price adjustment, post-offer institutional holdings, and the IPO size, however, positively affect offer values for both types of firms whereas the percentage of shares offered in the IPO negatively affects offer values of both type of firms [16].

Another form of resourcing firm development beyond private and public financings are strategic alliances. Strategic alliance may be defined as an agreement between two or more.

Companies with goals of pursuing an array of goals while remaining as independent companies. High tech firms such as companies in the biotechnology industry have used strategic alliances to gain access to know-how, competencies, and resources [23]. Biotechnology firms use alliances as inter-organizational learning devices on top of a way of accessing more financial resources and gaining legitimacy among biotechnology firms [24], [25]. In order to join knowledge and resources for successfully develop a new product, biotechnology companies take advantage of alliances and cooperation [23].

Research and development partnerships between pharmaceutical and biotech firms has a pattern of overall growth since the mid-1970s [26]. Alliances in biotech can be important to the point that Evens and Kaitin (2014) stresses the establishment of partnerships and alliances, intellectual property rights, and R&D investments as the biotech industry's progress factors [27]. Strategic alliances can get initiated from companies which are inclined towards knowledge sharing and R&D in order to invest on a new path or drug class when it's not company's core competency or in firm's comfort zone with goals of entering a new market or location via cooperation with firms in the desired drug class or geographical area [28].

In this context, mergers and acquisitions can be seen as an extension of strategic alliances whereby the acquired firm is sufficiently de-risked to be fully absorbed into the parent company. Next, we examine the role of IPOs in the context of access to research and development capital. We also explore and assess the degree of mismatch between the access to capital, operational efficiencies, capital market volatility, and valuation uncertainty.

## III. Methodology/Results

### A. Biotech IPOs

We used the Biocentury (2019) database which tracks over 1,300 public and 4,000 private biotechnology companies worldwide from 1995-present. We analyzed the 1,255 global biotechnology IPOs which raised $59.9 billion in financings during period 1994-2018 to explore patterns in access to capital, operational efficiencies, capital market volatility, and valuation uncertainty. Key variables identified include scientific publications, patents, private venture capital financings, initial public offerings (IPO), public follow on financings, strategic alliances (e.g., co-development, co-promotion), and mergers & acquisitions. Owing to the historic focus on high morbidity and mortality in oncology, cancer focused companies comprise 22% (280) of the total biotechnology IPOs. Owing to the historic focus on high morbidity and mortality in oncology, cancer focused companies In addition, 66% (831) of biotechnology IPOs were in the US owing to NASDAQ, the largest risk-based technology stock market. Despite this seeming stepwise integration and industry growth, the biotechnology IPO financing windows create significant volatility and uncertainty of access to capital in contrast to the steady progress of scientific insight and product development [12].

The exogenous shocks induced by financial volatility induces significant operational risk and requires a business model and resources to match the product development cycle (Figure 2). Of note, the number of biotech IPO filings by therapeutic area were significantly dominated by Oncology (see Figure 3); and by country which were predominantly US-based, albeit with increasing participation by China in recent years (see Figure 4).

This research uses correlation analysis (with 95% confidence) with the dependent variable 'IPOs' with regards to independent variables in order to be checked with respect to correlation (r), p-value (p), and R-squared (R2) [29]. The independent values considered in this research are as follows:

- *BLA*: Drug approvals through The Biologics License Application (BLA) [30].
- *NDA*: New Drug Approval (NDA) related approvals [31].
- *Orphan Drug Designations*: Number of drugs designated in the Orphan Drug Designation program which provides orphan status to drugs and biologics that are allocated for the safe and effective treatment, diagnosis or prevention of rare diseases [32].
- *Publications*: The number of Biotech related publications retrieved from Scopus website.
- *Patents*: The number of Patents in Biotech retrieved from Scopus.
- *NBI*: NASDAQ Biotechnology Index
- S&P 500: Market index with respect to the market capitalizations of five hundred large companies having common stock listed on any of NYSE, NASDAQ, or the CBOE BZX Exchange.
- *10 Year Treasury*: The return on investment, expressed as a percentage, on the U.S. government's debt obligations.
- *Amount Raised*: Refers to the total amount raised through IPOs in the respective year.

Each variable has data points corresponding to the years between 1994 and 2018. Correlation is the degree which two metric variables are related in a linear manner. In this case, (0-(-) 0.4 is considered as weak correlation; (-) 0.4- (-) 0.7 is considered medium correlation; and (-) 0.7- (-) 1.0 is considered as strong correlation. Negative correlations mean that an increase or decrease in the independent variable would result in the decrease or increase in the dependent value.

The p-value shows the significance ($p < 0.05$) of the hypothesis. This means that if the p-value for each of the tests is >0.05 we reject the hypothesis. However, if the p-value is < 0.05, we accept the hypothesis and consider the underlying assertion valid. Also, R2 refers to the percentage of 'IPOs' that can be explained by different independent variables. In other words, R2 determines the proportion of the variance in EV that can be predicted using the tested independent variable [9]. The descriptive statistics is shown in (Table 1).

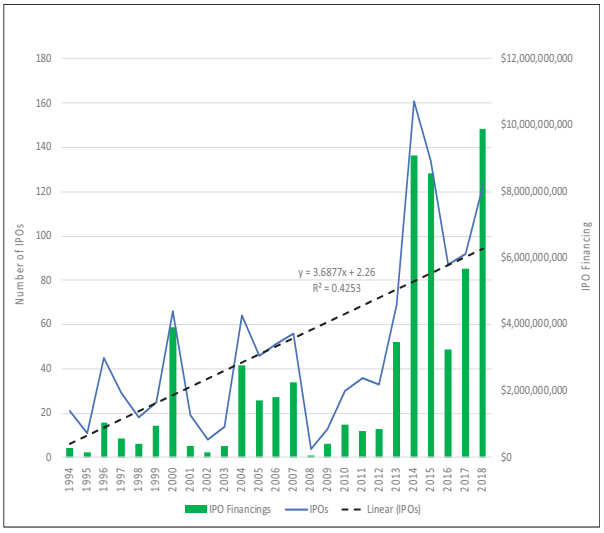


Figure 2: US Biotech IPOs and Financings, 1994-2018. Source: Biocentury (2019)

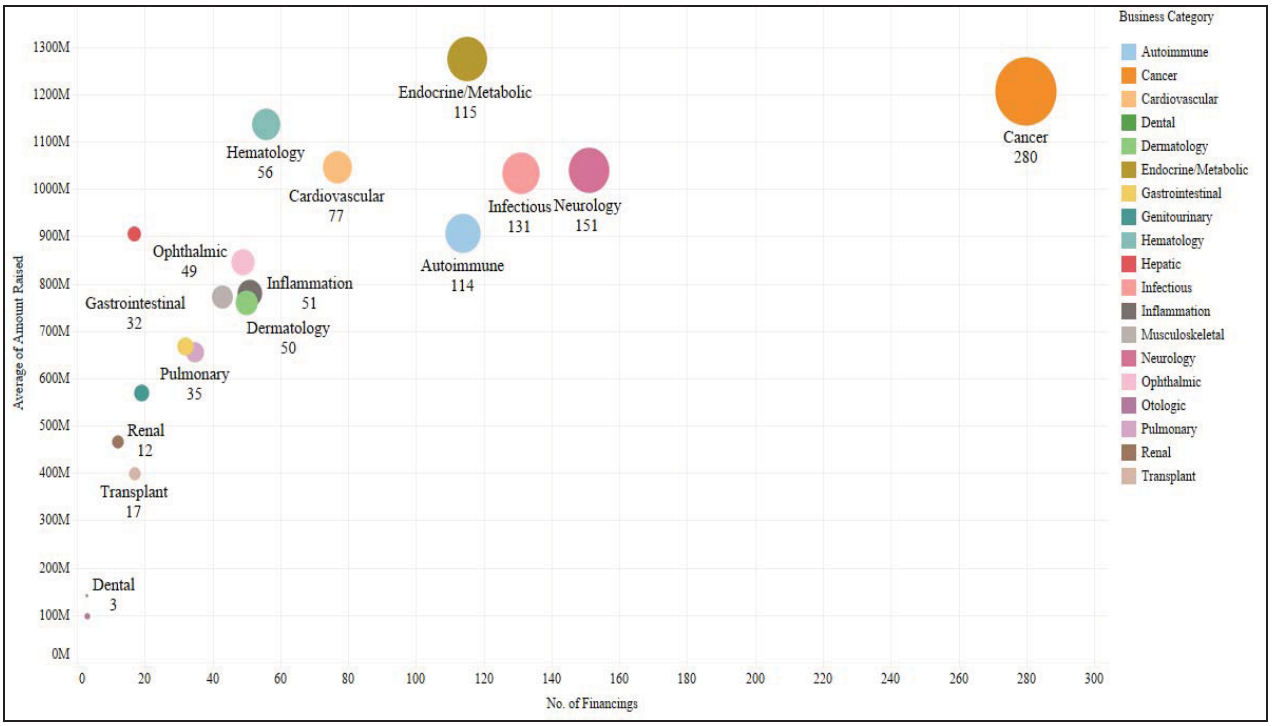


Figure 3: Biotech IPOs by Therapeutic Area, 1994-2018

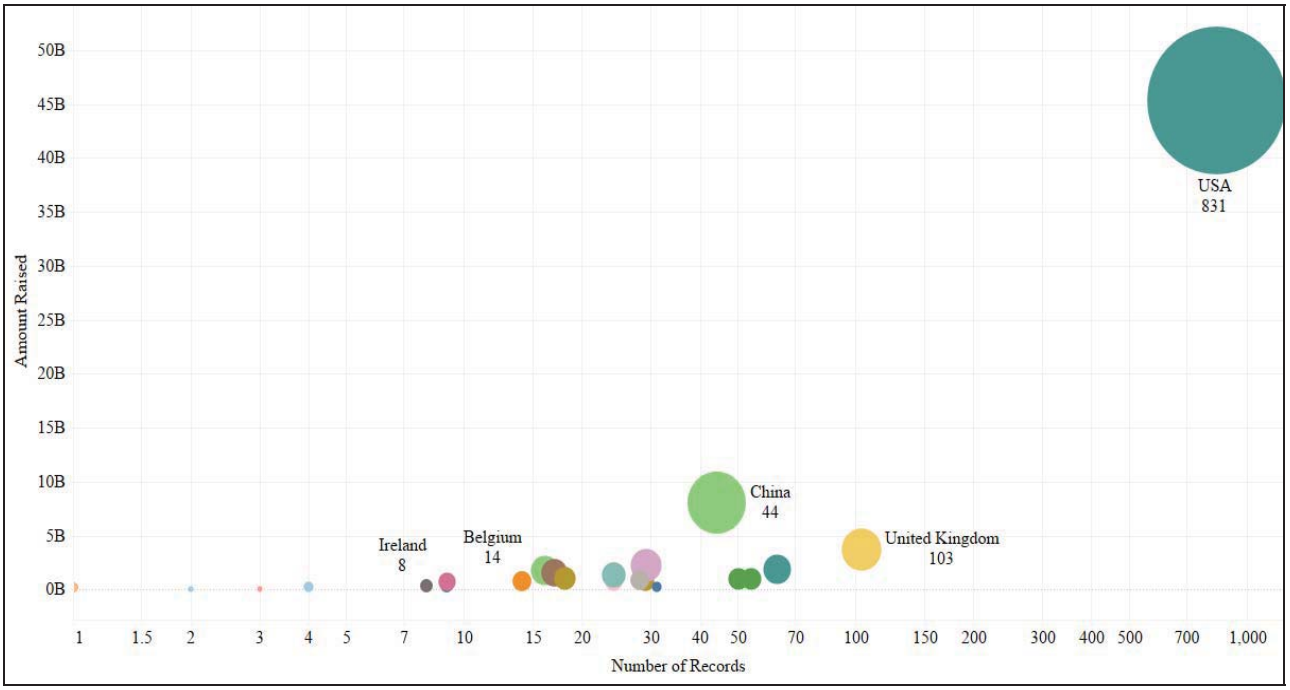


Figure 4: Biotech IPOs by Country, 1994-2018

TABLE 1: DESCRIPTIVE STATISTICS OF THE STUDIED VARIABLES

| | Mean | Std. Deviation | N |
|---|---|---|---|
| IPOs | 50.20 | 41.619 | 25 |
| Revenue | $673.48 | $309.554 | 25 |
| BLA | 5.52 | 3.501 | 25 |
| NDA | 24.96 | 8.853 | 25 |
| Orphan Drug Designation | 170.92 | 124.070 | 25 |
| Pubs | 90257.40 | 32061.065 | 25 |
| Patents | 8285.08 | 4730.262 | 25 |
| NBI | 758.64 | 628.397 | 25 |
| SandP500 | 301.58 | 122.576 | 25 |
| Treasury | 183.39 | 49.719 | 25 |
| Amount Raised | $2,394,021,613 | $2,922,413,042 | 25 |

As shown in Table 2 ,we found IPOs are highly correlated with Orphan drug designations, NBI, S&P 500, and amount of financing raised (all statistically significant), with the highest being the amount raised at 0.962. Publications, BLA, and 10-year treasury have moderate correlations; and patents and NDA have the lowest correlations.

Among BLA, NDA, and Orphan Drug designations (ODD), BLA has the highest correlation with the IPOs (0.678) which can be considered medium to almost high correlation. NDA has the weakest correlation with IPOs (0.378). All the correlation among these variables are statistically significant. There's also high inter-correlations between NDA and Orphan Drug Designations. Orphan Drug Designations also has high correlation with Publications, NBI, and S&P 500.

IPOs have a weak correlation with Patents and Publications, reflecting long lead times between discovery and development. Likewise, there's a high inter-correlation between patents and publications which reflects the relationship between patent disclosure and scientific publication. Revenue has medium correlation with IPOs (0.623) and high inter-correlation with variables such as Orphan drug designations, Treasury, patents and publications. As for the financial market related variables (NBI, S&P500, and Treasury), the stock market variables NBI and S&P 500 have high correlations with IPOs reflecting "financing windows" are strengthened by overall market strength. Finally, the amount raised has the highest correlation with the IPOs. Amount raised has high inter-correlations with BLA, NBI, and S&P500. Of note, the predictors account for explanation 97% of IPOs ($R^2 = 0.958$).

### B. *Gene Therapy Case Study*

To further explore how the biotechnology transforms knowledge into value, we evaluated the case of the gene therapy sub-sector of the biotechnology industry. Gene therapy is the therapeutic delivery of genetic material such as DNA into cells to compensate for abnormal genes or to make a beneficial protein. The EMA defines a gene therapy product as a "biological medicinal product that contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to humans to regulate, repair, replace, add or delete genetic sequence and its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence."[2][33]. In other words, if a patient has a missing or mutated gene, gene therapy can introduce a normal copy to restore the function of the protein. First used in a patient in 1990, there are over 2,000 clinical studies completed as of 2015, yielding 3 approved products as of 2019 [34]. As US FDA Commissioner Scott Gotlieb noted:

> *Gene therapy products now have the potential to cure intractable diseases, and fundamentally alter the trajectory of many other vexing illnesses. To advance these opportunities, the FDA plans to introduce additional new policy* ***guidance and other advances in our*** *drug development framework in 2019. Today, we want to take an opportunity to preview that policy agenda and offer some perspective on the focus of our policies over the coming year as it relates to these technologies* [35].

The antecedents to the growth in gene therapy is knowledge accumulation and dissemination represented by scientific publications and exclusivity shown by patent issuances. While the pace of scientific progress has been steady, however, the availability of capital due to the liability of newness and exogenous economic shocks (e.g., recession) has induced significant volatility into business model planning for gene therapy firms. Of note, private investment comprises 16% of financings for gene therapy companies. Public financings are 19%, comprised of IPOs which only account for 3% and follow on (secondary public offerings) represent 16% of sources of financing. On the other hand, strategic alliances and mergers and acquisitions represent 65% of financings as shown in (Table 3) and (Figure 5).

As a specific gene therapy company example, Avexis, Inc. was formed in 2010 to develop AVXS-101 (gene therapy) for the treatment of Spinal Muscular Atrophy (SMA), which is uniformly fatal by 2 years of age [36]. This disease is caused by a single genetic defect and Avexis has the goal of mitigating or treating this disorder using a single treatment gene therapy. Initial results presented in 2017 demonstrated that 15 of 15 (100%) patients were event-free at 13.6 months (versus an expected event-free survival rate based on the natural history of the disease of 25%). Early success allowed the company to complete two venture capital financings $10 million in January

2015, $65 million in September 2015, and IPO only 5 months later in February 2016, only to be purchased by multinational biopharmaceutical company, Novartis in April 2018 for $8.7 billion without any approved products. Of note, of the company's total financings of $1.1 billion, 7% or $75 million of company funding came from private venture capital; and 93% of invested capital came from multiple public financings, including only $105 million or 9% from the IPO. A summary of Avexis financings, valuation and acquisitions is shown in Table 2.

TABLE 2: AVEXIS, INC. FINANCING, VALUATION AND ACQUISITION (BIOCENTURY, 2019)

| Amount Raised | Financing Type | Date Completed | Post-Money Valuation | Share Price |
|---|---|---|---|---|
| $8,700,000,000 | Acquisition by Novartis | 4/9/18 | ---- | $218 |
| $460,003,680 | Follow-on | 1/16/18 | $3,721,598,112 | $102 |
| $287,787,500 | Follow-on | 6/20/17 | $2,233,406,560 | $70 |
| $158,618,752 | Follow-on | 9/8/16 | $952,596,198 | $35 |
| $105,558,820 | IPO | 2/10/16 | $458,570,800 | $20 |
| $65,000,000 | Venture | 9/8/15 | ---- | ---- |
| $10,000,000 | Venture | 1/6/15 | ---- | ---- |

TABLE 3: CORRELATIONS TABLE

| | | IPOs | Revenue | BLA | NDA | Orphan Drug Designations | Pubs | Patents | NBI | SandP500 | Treasury | Amount Raised |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pearson Correlation | IPOs | 1.00 | .623 | .687 | .378 | .750 | .689 | .416 | .871 | .800 | .626 | .962 |
| | Revenue | .623 | 1.00 | .636 | .024 | .903 | .988 | .875 | .820 | .790 | .990 | .622 |
| | BLA | .687 | .636 | 1.00 | .358 | .784 | .659 | .458 | .755 | .699 | .642 | .744 |
| | NDA | .378 | .024 | .358 | 1.00 | .202 | .032 | -.274 | .233 | .193 | -.026 | .405 |
| | ODD | .750 | .903 | .784 | .202 | 1.00 | .915 | .676 | .930 | .905 | .891 | .785 |
| | Pubs | .689 | .988 | .659 | .032 | .915 | 1.00 | .870 | .877 | .844 | .991 | .682 |
| | Patents | .416 | .875 | .458 | -.274 | .676 | .870 | 1.00 | .592 | .586 | .905 | .392 |
| | NBI | .871 | .820 | .755 | .233 | .930 | .877 | .592 | 1.00 | .926 | .822 | .877 |
| | SandP500 | .800 | .790 | .699 | .193 | .905 | .844 | .586 | .926 | 1.00 | .815 | .809 |
| | Treasury | .626 | .990 | .642 | -.026 | .891 | .991 | .905 | .822 | .815 | 1.00 | .630 |
| | Amount Raised | .962 | .622 | .744 | .405 | .785 | .682 | .392 | .877 | .809 | .630 | 1.00 |
| Sig. (1-tailed) | IPOs | . | .000 | .000 | .031 | .000 | .000 | .019 | .000 | .000 | .000 | .000 |
| | Revenue | .000 | . | .000 | .454 | .000 | .000 | .000 | .000 | .000 | .000 | .000 |
| | BLA | .000 | .000 | . | .039 | .000 | .000 | .011 | .000 | .000 | .000 | .000 |
| | NDA | .031 | .454 | .039 | . | .166 | .440 | .092 | .131 | .177 | .450 | .022 |
| | ODD | .000 | .000 | .000 | .166 | . | .000 | .000 | .000 | .000 | .000 | .000 |
| | Pubs | .000 | .000 | .000 | .440 | .000 | . | .000 | .000 | .000 | .000 | .000 |
| | Patents | .019 | .000 | .011 | .092 | .000 | .000 | . | .001 | .001 | .000 | .026 |
| | NBI | .000 | .000 | .000 | .131 | .000 | .000 | .001 | . | .000 | .000 | .000 |
| | SandP500 | .000 | .000 | .000 | .177 | .000 | .000 | .001 | .000 | . | .000 | .000 |
| | Treasury | .000 | .000 | .000 | .450 | .000 | .000 | .000 | .000 | .000 | . | .000 |
| | Amount Raised | .000 | .000 | .000 | .022 | .000 | .000 | .026 | .000 | .000 | .000 | . |

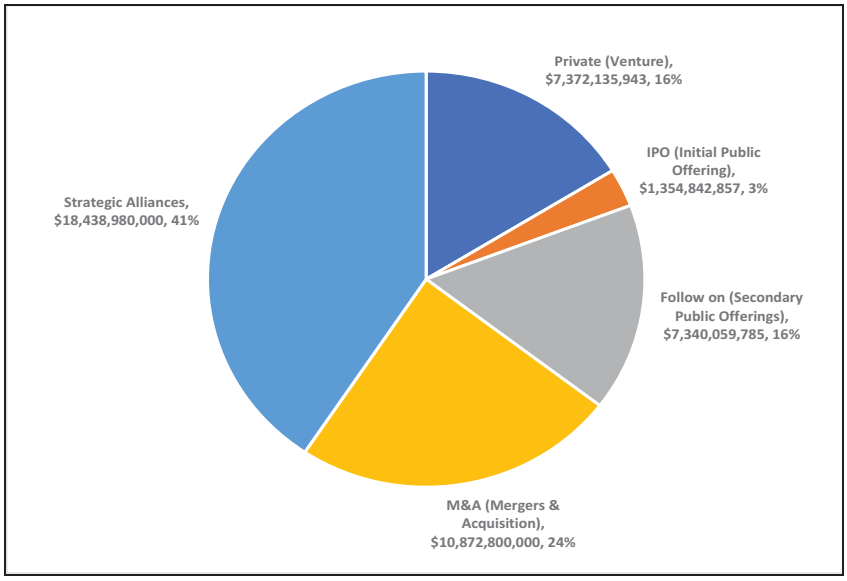


Figure 5: Gene therapy sources of financing, 1994-2018

TABLE 4: KEY INDICATORS OF GENE THERAPY INDUSTRY DEVELOPMENT

| Year | Publications | Patents | Private (Venture) | IPO (Initial Public Offering) | Follow on (Secondary Public Offerings) | M&A (Mergers & Acquisition) | Strategic Alliances | Total | US/EU Approvals |
|---|---|---|---|---|---|---|---|---|---|
| 1994 | 2,638 | 1,303 | | --- | --- | --- | --- | $0 | --- |
| 1995 | 3,443 | 1,930 | 30625000 | --- | $30,625,000 | --- | --- | $30,625,000 | --- |
| 1996 | 3,880 | 2,197 | | --- | --- | --- | --- | $0 | --- |
| 1997 | 4,521 | 2,404 | | --- | --- | --- | --- | $0 | --- |
| 1998 | 5,201 | 2,726 | $12,906,000 | --- | $12,906,000 | --- | --- | $25,812,000 | --- |
| 1999 | 6,095 | 3,291 | $8,768,000 | --- | $8,768,000 | --- | --- | $17,536,000 | --- |
| 2000 | 7,359 | 4,007 | $146,381,000 | $52,500,000 | $146,381,000 | --- | --- | $345,262,000 | --- |
| 2001 | 7,901 | 3,935 | $51,249,000 | --- | --- | --- | --- | $51,249,000 | --- |
| 2002 | 8,781 | 4,332 | | --- | --- | --- | --- | $0 | --- |
| 2003 | 9,677 | 4,351 | $109,968,646 | --- | $57,226,000 | --- | --- | $167,194,646 | --- |
| 2004 | 10,259 | 4,398 | $90,325,710 | --- | $90,325,710 | --- | --- | $180,651,420 | --- |
| 2005 | 11,351 | 4,769 | $95,195,200 | --- | $95,195,200 | --- | --- | $190,390,400 | --- |
| 2006 | 11,885 | 4,544 | $68,204,819 | --- | $68,204,819 | --- | --- | $136,409,638 | --- |
| 2007 | 12,359 | 4,217 | $51,678,000 | --- | $51,678,000 | --- | --- | $103,356,000 | --- |
| 2008 | 13,586 | 4,221 | | --- | --- | --- | --- | $0 | --- |
| 2009 | 14,085 | 3,963 | $51,641,667 | --- | $55,781,954 | --- | --- | $107,423,621 | --- |
| 2010 | 15,757 | 4,092 | $55,059,676 | --- | $55,059,676 | $162,900,000 | $163,900,000 | $436,919,352 | --- |
| 2011 | 16,836 | 4,189 | $96,767,640 | --- | $119,542,841 | --- | --- | $216,310,481 | --- |
| 2012 | 18,715 | 3,997 | $98,724,044 | --- | $143,724,044 | --- | --- | $242,448,088 | 1 |
| 2013 | 20,370 | 3,573 | $136,132,331 | $116,149,984 | $136,132,331 | --- | $50,000,000 | $438,414,646 | --- |
| 2014 | 22,450 | 3,765 | $592,747,359 | $174,800,004 | $592,747,359 | $155,700,000 | $435,700,000 | $1,951,694,722 | --- |
| 2015 | 24,580 | 4,027 | $824,882,603 | $404,250,000 | $824,882,603 | $40,900,000 | $5,037,900,000 | $7,132,815,206 | --- |
| 2016 | 24,913 | 4,114 | $497,184,507 | $193,685,000 | $497,184,507 | $120,800,000 | $120,800,000 | $1,429,654,014 | 1 |
| 2017 | 24,960 | 3,874 | $2,115,022,678 | $143,290,000 | $2,115,022,678 | $155,200,000 | $764,900,000 | $5,293,435,356 | 1 |
| 2018 | 18,805 | 3,384 | $2,238,672,063 | $270,167,869 | $2,238,672,063 | $10,237,300,000 | $11,865,780,000 | $26,850,591,995 | --- |

## IV. CONCLUSION

Access to multiple tranches of capital is critical for typically no revenue development stage biotechnology firms. While financing needs are monotonically increasing over multiple years in the product development approval cycle, the market for high risk, milestone driven biotechnology investment is significantly more volatile than the financial markets as a whole. In this paper, we analyzed the role of global biotechnology IPOs, as well as other sources of financings, for research and development capital. We also explored and assessed the degree of mismatch between the access to capital, operational efficiencies, and how firms solve the potential unmet capital requirements.

We concluded that the financings data in the biotechnology industry and gene therapy subsector case study reinforce that while important and highly visible milestone in company development, IPOs represent a small fraction in the continuum of access to resources for research and commercialization. In this context, the biotechnology industry is resolving the asymmetric information and binary risk present in nascent technologies with a stage-gate approach and multiple sources of capital. In other words, development stage biotechnology firms represent a continuum of real options—defined as the right but not the obligation to make a series of business decisions (e.g., incrementally invest to advance a drug candidate from Phase II to Phase III clinical trials) by investors and/or strategic alliance partners and acquirers (Figure 6) [13], [37].

The implications for investors is that while not a guarantee, strategic alliances represent an important signaling function in assessing firms with novel technologies and significant information asymmetry (i.e., a small firm successfully obtaining a strategic alliance with a large pharmaceutical firm after due diligence represents a de-risking event)[38]. Another implication for investors is that exogenous economic shocks, independent of company progress, may induce disproportionate changes in equity value.

The practical implication for companies is to conduct financings to the maximum amounts available in 'open window' periods. In other words, the risk of running out of capital is generally higher than the cost of dilution. For large multinational pharmaceutical companies who face a continuous cycle of pipeline renewal driven by patent expiries, the implication is that strategic alliances and mergers and acquisitions represent a strategic network approach to research and development which creates significant sources of operational and financial leverage [39]. This research serves as an addition to the technology management body of knowledge for multinational pharmaceutical companies.

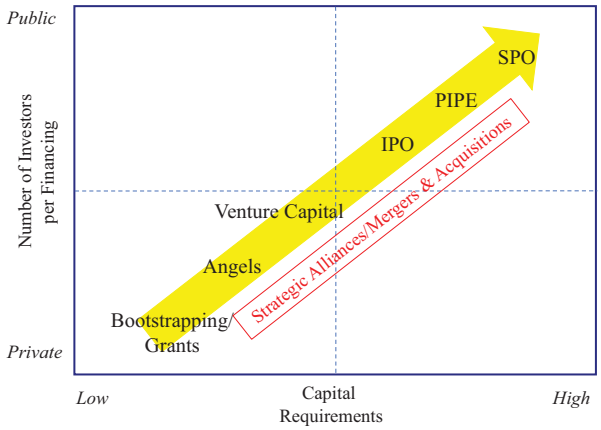


Figure 6: Bio-financing Continuum

Limitations of this study include the evolving role of international markets in the exploitation of new biology insights into companies, increasingly occurring in China and Europe (i.e., to what extent is the biotechnology business model changing from the current US-based paradigm). An interesting extension to this study would be to explore the role of signaling in biotechnology IPOs to investors and strategic alliance partners. Moreover, further research is needed into th the nature of patents in the complex biopharmaceutical industry [40].

In sum, we believe this study contributes to the research literature by expanding and extending insights into the role of global biotechnology IPOs, as well as other sources of financings, for research and development capital. We also explored and assessed the degree of mismatch between the access to capital, operational efficiencies, and how firms solve the potential unmet capital requirements. Further, our integration of financings and strategic alliances provides a lens from which to explore emerging varieties of small and large company innovation in the biopharmaceutical industry.

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